

REMARKS

Reconsideration of the subject matter identified in caption, pursuant to and consistent with 37 C.F.R. §1.112 in light of the remarks which follow is respectfully requested.

As correctly indicated in the Office Action Summary, claims 42-59 are pending in the instant application. Claims 42, 54 and 56, 57 and 58 have been amended herein, in order to more clearly recite an endpoint for the recited process. Basis for this amendment may be found at least throughout the specification and claims as filed, especially on page 17, lines 20-21. Thus, no prohibited new matter has been introduced.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 42-59 stand rejected under 35 U.S.C. §112, first paragraph, as purportedly containing subject matter which was not adequately described in the specification. Specifically, the Office Action asserts that the specification and the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez (as submitted September 18, 2000) fail to demonstrate a connection between the claimed compounds or the *in vitro* data provided in the declaration and the various "retinoid" compositions disclosed in the references cited in the declaration. This rejection is respectfully traversed.

Applicants respectfully submit that a connection between the claimed compounds and the retinoids disclosed in the references cited in the declaration has been demonstrated. To this end, Applicants provide further explanation of the

results of the experiments disclosed in the specification and in the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez. Results obtained with the compounds disclosed in Example 2, especially 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2A-1-benzofuran-6-carboxylic acid, of the specification in the F9 test ($AC_{50} < 10000$ nM) demonstrate that this compound is a RAR-agonist. Furthermore, the compound of Example 2, was observed to activate the production of plasminogen (see Bailly, *Skin Pharmacol.* (1990) 3:256-67). This compound transactivates RARs, with the specific percentage of activation for RAR α of 96%, for RAR β of 87% and for RAR γ of 78%. This compound also has the particularity to bind and transactivate the RXR receptor ($K_d < 10000$ nM). Consequently, this particular retinoid is known as a panagonist having both RAR and RXR activity.

In addition, the compound of Example 6, 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid, (pages 39-40 of the present specification demonstrates RAR activity. Specifically, Applicants refer the Examiner to the F9 test ($AC_{50} < 10000$ nM) and the transactivation test (percent of activation for RAR α was 45.5%, for RAR β was 57.3% and for RAR γ of 33.8%).

Again, Applicants would like to turn the Examiner's attention to the Declaration pursuant to 37 C.F.R. §1.132 by Dr. Michel Demarchez, which sets forth experimentation performed on the RXR receptor. The transactivation test, which measures the RXR activity induced by the addition of 10 μ M of the tested compound, is set forth in the Declaration. Also found in the Declaration is the RXR transactivation AC_{50} , which represents the quantity of the tested compound

required to induce 50% of the RXR activity. This experimentation has been conducted on the RXR α receptor.

Thus, based on the above remarks, Applicants respectfully submit that the efficacy of retinoid compounds as pharmaceutical agents is accepted in the art. Applicants further submit that it is reasonable to conclude that they will exhibit desirable pharmacological properties and be useful in the treatment of the recited conditions, and that the compounds of the claimed invention may be used in treatment of the claimed conditions. Accordingly, withdrawal of the rejection of claims 42-59 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH


Claims 42-59 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. Specifically, the Office Action asserts that the process steps and the endpoint of the process recited in the method claims are unclear. Independent claims 42, 54, 56, 57 and 58 have been amended to additionally recite compounds that are administered "for a time and under conditions effective to activate the retinoic acid receptor". Thus, Applicants submit that the claims, following the entry of the present amendment, recite a clear endpoint for the recited process. Thus, Applicants submit that this rejection has been traversed.

CONCLUSION

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding, the Examiner is respectfully requested to contact the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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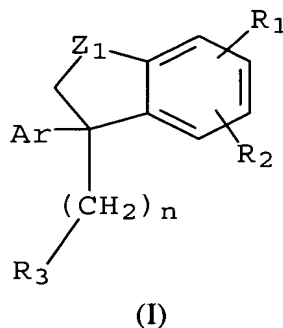
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Date: February 22, 2002

Attachment to Reply and Amendment

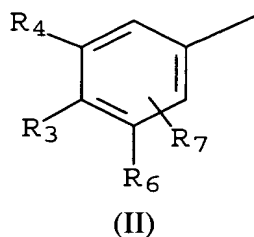
Marked-up Claims 42, 54, 56, 57 and 58

42. (Once Amended) A method for the treatment of a dermatological condition which is selected from the group consisting of: a keratinization disorder which affects differentiation and proliferation; a keratinization disorder which is not associated with differentiation and proliferation; a keratinization disorder having an inflammatory and/or immunoallergic component; dermal or epidermal proliferation; bullosis or a collagen disorder; light-induced or chronological aging of the skin; actinic keratosis or pigmentation; chronological or actinic aging associated pathology; stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids; a cicatrization disorder; vibices; a sebaceous associated disorder; a viral related skin disorder; alopecia; a dermatological condition having an immunological component; and a skin disorder attributable to exposure to UV radiation; in a subject in need of said treatment, said method comprising administering to said subject for a time and under conditions effective to activate the retinoic acid receptor, in an amount effective to treat said condition, at least one compound having the formula (I) below:

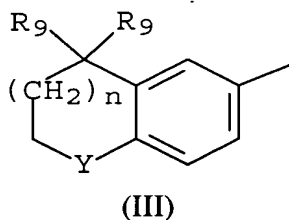


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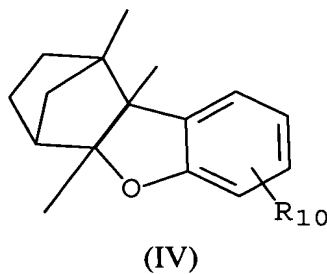
- Ar represents
- either the radical of formula (II) below:



- or the radical of formula (III) below:



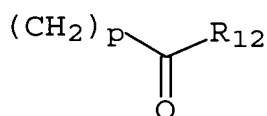
- or the radical of formula (IV) below:



- R₁ represents an atom or a radical selected from the group consisting of:
 - (i) the -CH₃ radical,
 - (ii) the radical -(CH₂)_p-O-R₁₁'

(iii) a radical $-OR_{11}'$

(iv) a radical



(v) a radical $-S(O)_tR_{13}$,

R_{11} , R_{12} , R_{13} , p and t have the meanings given below,

- R_2 represents a hydrogen atom, a halogen atom, an alkyl radical or the radical

$-OR_{11}$,

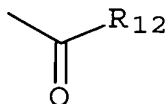
R_{11} has the meaning given below,

- R_3 represents an atom or a radical selected from the group consisting of:

(i) an atom or a radical selected from the group consisting of a hydrogen atom, an alkyl radical, an alkenyl radical, an alkynyl radical, an aryl radical, a monohydroxyalkyl radical, a polyhydroxyalkyl radical, a polyether radical, a cyano radical and a radical $-O-R_{11}$,

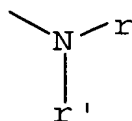
R_{11} has the meaning given below,

(ii) a radical



R_{12} has the meaning given below,

(iii) a radical



r and r' have the meanings given below,

- Z_1 represents O, S or NR' ,
- m is an integer between 0 and 10, wherein R_4 , R_5 , R_6 and R_7 may be identical or different, and are selected from the group consisting of:

- (i) a hydrogen atom,
- (ii) an alkyl radical having at least 4 carbon atoms, wherein the carbon attached to the phenyl radical is substituted with at least two carbon atoms,

- (iii) a cycloalkyl radical,
- (iv) a radical $-(Z_2)_n-(\text{CH}_2)_q-\text{CO}-R_{12}$,
- (v) a radical $-Z_3-R_{11}$,

wherein at least one of the radicals R_4 , R_5 , R_6 and R_7 is an alkyl radical as defined in (ii) or a cycloalkyl radical (iii),

Z_2 , Z_3 , R_{11} , R_{12} , n and q have the meanings given below,

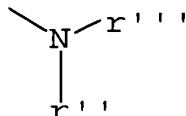
R_8 and R_9 represent lower alkyl radicals,

R_{10} represents a lower alkyl radical, a radical $-\text{OR}_{11}$ or a polyether radical,

R_{11} , which may be identical or different, represents a hydrogen atom, a lower alkyl radical, an aryl radical, an aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical or a lower acyl radical,

R_{12} , which may be identical or different, represents:

- (a) a hydrogen atom, an alkynyl radical, an alkenyl radical, an alkyl radical or a heterocycle,
(b) a radical



r'' and r''' having the meaning given below

- (c) a radical $-OR_{13}$

R_{13} , which may be identical or different, represents a hydrogen atom, an alkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar, amino acid or peptide residue,

R' , which may be identical or different, represents a protecting group for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical or an optionally substituted aryl radical or an amino acid, peptide or sugar residue,

r and r' , which may be identical or different, represent protecting groups for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

r'' and r''' , which may be identical or different, represent a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr' , CHOH, CO, SO or SO_2 ,

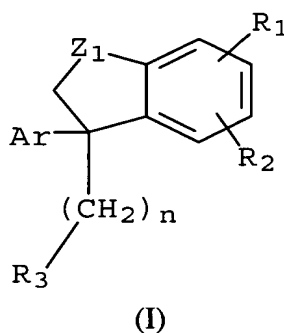
Z_2 represents O, S or NR' ,

Z_3 represents O or S,

n, which may be identical or different, is equal to 0 or 1; p, which may be identical or different, is equal to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an integer between 0 and 10,

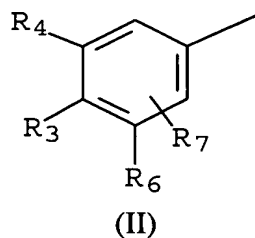
or a salt or isomer thereof.

54. (Once Amended) A method for the treatment of an ophthalmological disorder in a subject in need of said treatment, said method comprising administering to said subject for a time and under conditions effective to activate the retinoic acid receptor, in an amount which is therapeutically effective against said ophthalmological disorder, at least one compound having the formula (I) below:

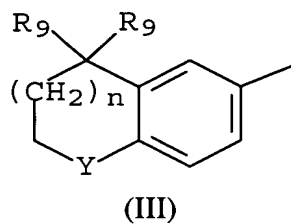


in which:

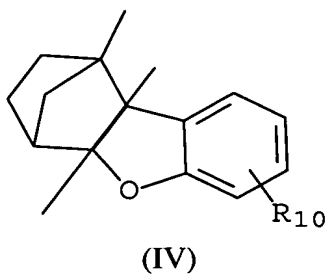
- Ar represents
- either the radical of formula (II) below:



- or the radical of formula (III) below:

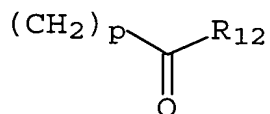


- or the radical of formula (IV) below:



- R₁ represents an atom or a radical selected from the group consisting of:

- (i) the -CH₃ radical,
- (ii) the radical -(CH₂)_p-O-R₁₁'
- (iii) a radical -OR₁₁'
- (iv) a radical



(v) a radical $-S(O)_tR_{13}$,

R_{11} , R_{12} , R_{13} , p and t have the meanings given below,

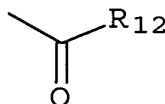
- R_2 represents a hydrogen atom, a halogen atom, an alkyl radical or the radical $-OR_{11}$,

R_{11} has the meaning given below,

- R_3 represents an atom or a radical selected from the group consisting of:
 - (i) an atom or a radical selected from the group consisting of a hydrogen atom, an alkyl radical, an alkenyl radical, an alkynyl radical, an aryl radical, a monohydroxyalkyl radical, a polyhydroxyalkyl radical, a polyether radical, a cyano radical and a radical $-O-R_{11}$,

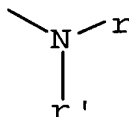
R_{11} has the meaning given below,

(ii) a radical



R_{12} has the meaning given below,

(iii) a radical



r and r' have the meanings given below,

- Z_1 represents O, S or NR' ,
- m is an integer between 0 and 10, wherein R_4 , R_5 , R_6 and R_7 may be identical or different, and are selected from the group consisting of:

(i) a hydrogen atom,
(ii) an alkyl radical having at least 4 carbon atoms, wherein the carbon attached to the phenyl radical is substituted with at least two carbon atoms,

- (iii) a cycloalkyl radical,
(iv) a radical $-(Z_2)_n-(CH_2)_q-CO-R_{12}$,
(v) a radical $-Z_3-R_{11}$,

wherein at least one of the radicals R_4 , R_5 , R_6 and R_7 is an alkyl radical as defined in (ii) or a cycloalkyl radical (iii),

Z_2 , Z_3 , R_{11} , R_{12} , n and q have the meanings given below,

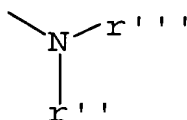
R_8 and R_9 represent lower alkyl radicals,

R_{10} represents a lower alkyl radical, a radical $-OR_{11}$ or a polyether radical,

R_{11} , which may be identical or different, represents a hydrogen atom, a lower alkyl radical, an aryl radical, an aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical or a lower acyl radical,

R_{12} , which may be identical or different, represents:

- (a) a hydrogen atom, an alkynyl radical, an alkenyl radical, an alkyl radical or a heterocycle,
(b) a radical



R'' and R''' having the meaning given below

- (c) a radical $-OR_{13}$

R_{13} , which may be identical or different, represents a hydrogen atom, an alkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar, amino acid or peptide residue,

R' , which may be identical or different, represents a protecting group for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical or an optionally substituted aryl radical or an amino acid, peptide or sugar residue,

r and r' , which may be identical or different, represent protecting groups for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

r'' and r''' , which may be identical or different, represent a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr' , CHOH, CO, SO or SO_2 ,

Z_2 represents O, S or NR' ,

Z_3 represents O or S,

n , which may be identical or different, is equal to 0 or 1; p , which may be identical or different, is equal to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an integer between 0 and 10,

or a salt or isomer thereof.

56. (Amended) A method for the treatment of a dermatological condition which is selected from the group consisting of: a keratinization disorder which affects differentiation and proliferation; a keratinization disorder which is not associated with differentiation and proliferation; a keratinization disorder having an inflammatory and/or immunoallergic component; dermal or epidermal proliferation; bullosis or a collagen disorder; light-induced or chronological aging of the skin; actinic keratosis or pigmentation; chronological or actinic aging associated pathology; stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids; a cicatrization disorder; vibices; a sebaceous associated disorder; a viral related skin disorder; alopecia; a dermatological condition having an immunological component; and a skin disorder attributable to exposure to UV radiation; in a subject in need of said treatment, said method comprising administering to said subject for a time and under conditions effective to activate the retinoic acid receptor, in an amount effective to treat said condition, a compound selected from the group consisting of 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid, 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid and 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid.

57. (Amended) A method for the treatment of arteriosclerosis or hypertension in a subject in need of said treatment, said method comprising administering to said subject for a time and under conditions effective to activate the retinoic acid receptor, in an amount which is therapeutically effective against

arteriosclerosis or hypertension, a compound selected from the group consisting of 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid, 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid and 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid.

58. (Amended) A method for the treatment of insulin-dependent diabetes in a subject in need of said treatment, said method comprising administering to said subject for a time and under conditions effective to activate the retinoic acid receptor, in an amount which is therapeutically effective against insulin-dependent diabetes, a compound selected from the group consisting of 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid, 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid and 3-methyl-3-(5, 6, 7, 8-tetrahydro-5, 5, 8, 8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid.